



**Stand Up To Cancer
Dream Team Announcement
Fact Sheets**

Title: “Targeting PI3K in Women’s Cancers”

Overview:

This project focuses on frequent mutations that occur in a set of genes that regulate the PI3K pathway, which is a complex signaling cascade that, in concert with other signaling networks, regulates cell survival and growth. The scientists involved in this Dream Team are the pioneers who discovered the PI3K pathway and validated its role in human cancers, and they will focus on breast, ovarian and endometrial cancers, all of which have the PI3K mutation.

A number of drugs to inhibit this pathway have been developed and currently are in clinical trials. However, as with other “targeted” therapies, only a fraction of patients who enroll in these trials benefit, and it is not possible to predict which patients will respond positively. This means that many women will be given treatments that have no benefit to them or could cause unnecessary complications.

The goal of this Dream Team is to discover approaches that will predict which patients will respond positively to PI3K inhibitors. If successful, this will accelerate personalized cancer treatment that can be incorporated into standard practice.

Significance: The PI3K pathway is mutated in more cancer patients than any other, and these mutations are the most frequent events in women’s cancers, making it an attractive molecular target for agents that inhibit these genetic aberrations. If successful, this project will allow clinicians to use biomarkers and imaging techniques to predict which patients will benefit from PI3K pathway inhibitors and lead to the development of therapeutic combinations that will hit multiple targets in the complex pathways that contribute to cancer cell growth.

This work will help assure that these therapies are given to patients who will benefit from them, and it will also increase the overall pace of clinical trials targeting PI3K inhibitors.

Specific Research Goals:

- Develop molecular markers/imaging techniques that predict the subset of cancers likely to respond to PI3K pathway inhibitors.
- Use markers to design/conduct clinical trials in study in patients exhibiting the specific mutation to determine the drug’s efficacy.
- Develop and conduct clinical trials using PI3K pathway inhibitors and other targeted drugs.

The problem is that even though we know this pathway is commonly mutated in women's cancers, every cancer that develops doesn't necessarily have the same component missing or deleted or amplified. So even though there's a whole set of pieces of the puzzle that fit together, different patients have aberrations in different pieces of the puzzle. But the final conclusion is that they get cancer because of it.

An analogy I like to make is that if you have a problem with one of the electrical circuits in your house and you want to turn off the circuit breaker so you can fix it, and you don't know the wiring diagram of your house, you would be going to the basement, flipping things off and then back to the third floor a dozen times or more before you get the right answer... If you have a wiring diagram, which is what we have been working on for the last 20 years or so, then you can make an educated guess--this is the circuit breaker, this should work for this event. Then when the patient comes in, we can test them and if see a particular event, we can say, this is the drug for you.

-- Team Co-Leader Charles L. Sawyers, M.D., director, Human Oncology and Pathogenesis Program, Memorial Sloan-Kettering Cancer Center

Dream Team Leaders	Leader: Lewis C. Cantley, Ph.D. , chief, division of signal transduction, Beth Israel Deaconess Medical Center (Boston, MA)	Co-Leaders: Gordon B. Mills, M.D., Ph.D. , chair, department of systems biology, University of Texas M.D. Anderson Cancer Center (Houston, TX) Charles Sawyers, M.D. , director, Human Oncology and Pathogenesis Program, Memorial Sloan-Kettering Cancer Center (New York, NY)
Dream Team Principals	Carlos Arteaga, M.D. , director, Vanderbilt Breast Cancer Program, Vanderbilt University Medical Center (Nashville, TN), José Baselga, M.D. , chairman and professor of medicine, Vall D'Hebron Institut of Oncology, Vall d'Hebron University Hospital (Barcelona, Spain); Thomas M. Roberts, Ph.D. , co-chair, department of cancer biology, Dana-Farber Cancer Institute (Boston, MA) Ramon Parsons, M.D., Ph.D. , Avon Professor of pathology and medicine, Institute for Cancer Genetics and the Herbert Irving Comprehensive Cancer Center, Columbia University (New York, NY)	
Dream Team Advocates	Ruth Fax , patient advocate, Dana-Farber Cancer Institute, Breast Cancer SPORE (Boston, MA), Elizabeth Frank , lead patient advocate, Dana-Farber Cancer Institute/Harvard Cancer Center, Breast SPORE (Boston, MA), Judi Hirshfield-Bartek, R.N., M.S., O.C.N. , clinical nurse specialist, Beth Israel Deaconess Medical Center, Breast Care Center (Boston, MA), Sara Weiss , advocate, Dana-Farber Cancer Institute (Boston, MA), Patricia Lee , Vanderbilt-Ingram Cancer Center (Nashville, TN) Don Listwin , Canary Foundation (Palo Alto, CA) Jane Perlmutter , Ph.D., University of Texas M. D. Anderson Cancer Center (Houston, TX)	

Title: “Cutting Off the Fuel Supply: A New Approach to the Treatment of Pancreatic Cancer”

Overview:

As the fourth leading cause of cancer death in the United States, pancreatic cancer remains one of the most deadly forms of cancer. Over 90 percent of patients die within the first year of diagnosis. Recent advancements have had little impact, and a new approach is desperately needed.

Scientists have suggested the possibility of “starving” cancer cells to death by depriving them of a specific nutrient that they require for survival. Recent studies have demonstrated that most cells acquire mutations causing them to become addicted to a continual supply of nutrients to produce the energy needed for survival and proliferation. In most cancers, this nutrient is glucose.

Using modern tumor imaging, it is possible to monitor a tumor’s glucose utilization and such tests are now routinely used in clinical practice. In most cases, the more glucose a tumor is using, the more advanced the tumor and the greater likelihood of spread. Similarly, if a tumor is using less glucose as a response to chemotherapy, then it is a good indication that the tumor is responding to treatment.

Pancreatic cancer presents a unique challenge because it is addicted to another molecule, glutamine, rather than glucose. Glutamine is an amino acid that helps build muscle mass and is used by some cells for energy. When cancer feeds or metabolizes excess amounts of glutamine, it can lead to extreme weight loss by robbing other cells of this important nutrient, a condition from which many pancreatic cancer patients suffer. In addition, the waste that is a by-product of this process generates an intense reaction from surrounding normal cells, which then secrete growth factors that help tumor cells grow. Cancers that use excess glutamine are often resistant to standard forms of chemotherapy, another characteristic of pancreatic cancer.

Specific Research Goals:

- The goal of this Dream Team is to develop tests using advanced imaging techniques to determine what nutrients pancreatic cancer cells require to fuel their growth and survival. Understanding the cell’s fuel supply will help scientists to develop more individualized treatments with fewer side effects.
- This Dream Team will immediately begin a series of clinical trials designed to deprive pancreatic tumors of crucial nutrients. The team will test the drugs in combination with existing standard chemotherapy, with the hope to increase the percentage of pancreatic cancer patients surviving beyond one year while improving quality of life.

Pancreatic cancer is a bad disease with a lot of pain and other negative effects... Many of us see patients with it every single day and we get tired of not being able to do something dramatic for them. We can do a little, help with pain, lengthen survival some, but we want to do something dramatic. It is going to take a tremendous amount of real thinking power to

make that difference, so it is a dream come true to be able to put this team together to work towards this goal.

-- Team Leader Daniel D. von Hoff, M.D., F.A.C.P., senior investigator and physician in chief, Translational Genomics Research Institute (TGen)

Dream Team Leaders	Leader: Craig B. Thompson, M.D., director, Abramson Cancer Center, University of Pennsylvania (Philadelphia, PA)	Leader: Daniel D. von Hoff, M.D., F.A.C.P., senior investigator and physician in chief, , Translational Genomics Research Institute (TGen) (Phoenix, AZ)
Dream Team Principals	Chi Dang, M.D., Ph.D., vice dean for research, Johns Hopkins University School of Medicine (Baltimore, MD), Joshua Rabinowitz, M.D., Ph.D., assistant professor of chemistry and integrative genomics, Princeton University (Princeton, NJ), Geoffrey Wahl, Ph.D., past president, AACR	
Dream Team Advocates	Barton Kamen, scientific director of the Leukemia and Lymphoma Society (White Plains, NY) Howard Young, Randall Katz, Julie Fleshman, president and CEO of the Pancreatic Cancer Action Network (El Segundo, CA)	

Title: “Bioengineering and Clinical Applications of Circulating Tumor Cells Chip”

Overview:

Cancers arise within the cells of an organ, such as the breast or pancreas, but cause death by disseminating throughout the bloodstream, spreading – or metastasizing – to the bone, liver, lungs or brain.

Cancer cells that spread from the primary tumor can be found in the blood of patients with cancer. These circulating tumor cells (CTCs) are extraordinarily rare – there is *one per one billion* normal cells. The ability to detect and analyze them would allow for significant advances in detecting and treating cancers as well as understanding the fundamental mechanisms by which cancers spread.

Technology available to date has not proved to be either sensitive or reliable enough to allow detection and analysis of these cells or to be useful in guiding treatment decisions.

In this project, a collaboration of clinicians, bioengineers and molecular biologists has developed a novel and radically different approach to detecting and isolating CTCs. This technology takes advantage of microscopic fluid dynamics to construct a Chip with 100 times greater sensitivity than existing technologies. The CTC-Chip is the size of a business card and contains 78,000 microscopic columns, each coated with material capable of attaching to CTCs while allowing normal blood cells to flow through unimpeded.

The CTC-Chip can capture approximately 200 CTCs from a teaspoon of blood taken from a cancer patient, making these cells available for scientific analysis, providing an important tool for clinical investigation, and ultimately leading to improved clinical care for patients with cancer.

Significance: The potential clinical applications of this technology are widespread and have the potential to revolutionize the ways in which cancers are detected and treated. The CTC-Chip could make it possible to analyze cancers of the internal organs in real time, non-invasively, both at the time of diagnosis and throughout treatment. This would enable clinicians to match patients to effective therapies and monitor the response to treatments.

Specific Research Goals:

- Optimize the technology of the CTC-Chip to make it more sensitive and assure that it can be used reliably and efficiently in a large-scale clinical setting.
- Conduct clinical trials to assess the value of the Chip in detecting cancers early or monitoring tumor response to treatment. The trials will involve a wide range of cancers (including breast, pancreatic, prostate and colon).
- An additional goal for the CTC-Chip is to make it sufficiently sensitive to detect cancers at an earlier stage. Studies indicate that tumors may start shedding CTCs into the bloodstream long before they actually metastasize to distant organs, opening the door for early detection and screening strategies.

When patients develop cancer and it has spread, there is often no good way of following the cancer during treatment. You have a biopsy that is done early in your treatment, and then we somewhat improvise with different treatments, some work, some don't, but it's really a bit of guess work.

If you had a way of doing a blood test and questioning the tumor cells, looking at what genes are abnormal, whether they are likely to respond to this drug versus that drug, and being able to do that repeatedly through the course of a patient's treatment, then you really have a way of following the kind of interventions we do in real time. That would really direct the kind of treatments, particularly the new and more focused treatments, the smart drugs or targeted treatments that we have for cancer.

The other clinical application is that we're getting indications that cancers tend to send out these cells into the blood relatively early when they become invasive. The great hope is that we could use this eventually to pick up cancer earlier, at a time when it could still be cured.

I think the excitement about bringing technology into a question like this is all of a sudden you can ask questions you could never ask before. We all know that cancer spreads; it goes from the breast to the lungs, or from the colon to the liver, but you could never see that transit. You could never see the cells in the act of spreading, which is what we can do now. The very questions that you can ask, some very simple, some very profound, are all dependent on technology.

-- Team Leader Daniel A. Haber, M.D., Ph.D., director, Massachusetts General Hospital Cancer Center

Dream Team Leaders	Leader: Daniel A. Haber, M.D., Ph.D. , director, Massachusetts General Hospital Cancer Center (Boston, MA)	Co-Leader: Memhet Toner, Ph.D. , professor, biomedical engineering, Massachusetts General Hospital, Harvard Medical School (Boston, MA)
Dream Team Principals	Sangeeta N. Bhatia M.D., Ph.D. , professor of HST/EECS (health sciences and technology/electrical engineering and computer science), Massachusetts institute of Technology (Boston, MA), Mark G. Kris, M.D. , chief of thoracic oncology service, Memorial Sloan Kettering Cancer Center (New York, NY), Bruce E. Johnson, M.D. , professor of medicine, Dana-Farber Cancer Institute (Boston, MA), Roy S. Herbst, M.D., Ph.D. , professor of medicine and cancer biology, University of Texas MD Anderson Cancer Center (Houston, TX)	
Dream Team Advocates	Jeane Ungerleider, Ph.D., L.I.C.S.W. , director, psychological services, Boston IVF (Brookline, MA), Becky Douglas , founder, Douglass Charitable Foundation	

Title: “Bringing Epigenetic Therapy to the Forefront of Cancer Management”

Overview:

Researchers have discovered that there are additional layers of material outside of the DNA that regulate, or turn on and off, genes. These epigenomes, as they are known, have been the focus of a rapidly emerging, important new area of cancer research. Investigators have determined that inappropriate epigenetic activity contributes significantly to cancer causation and growth, and that unlike mutations in the DNA, these changes can be reversed. This opens the door to research that could potentially regulate this activity or return the affected genes to normal function even after they have become defective.

The overarching goal of this Dream Team Project is to bring the promise of epigenetic therapy to clinical practice; it will focus on breast, colon and lung cancers as well on leukemia.

Specific Research Goals:

- Developing biomarkers that can predict and monitor the efficacy of cancer epigenetic therapies.
- Self-renewing cancer cells, often called cancer stem cells are of great interest to researchers; they often become resistant to currently available drugs. Many scientists believe that it is essential to develop new therapies that target these cancer stem cells in order to improve the long-term outcomes of cancer treatment. The team will build on intriguing preliminary data suggesting that reversal of gene “silencing” leads to a loss of cancer stem cells.
- Develop a clinical trial that utilizes a new second generation epigenetic drug that may be able to more effectively inhibit the epigenetic changes involved in cancer causation.

What has really happened over the last few years is we have gained an ability to look at cells, both normal cells and cancer cells in their entirety, and note the sorts of molecular changes that occur in the formation of a cancer cell. This will allow us to think more clearly about prevention and therapeutic strategies.

What we find happens in cancer cells is that the packaging gets messed up so the genes get mispackaged. Some of them get closed up into boxes where they cannot be used and others get activated where they shouldn't be used. Importantly, we have drugs that we think can undo the bows and open the boxes and allow the appropriate genes to get out and do their thing. This is a completely novel way of looking at cancer therapy.

-- Team Co-Leader Peter A. Jones, Ph.D., distinguished professor of urology, biochemistry and molecular biology, University of Southern California

Your DNA is like a hard drive. You've got all the information in it to read out and do everything you can do with it, but without packaging and without sufficient software you can't instruct that DNA when to do X and when to do Y and Z. Cancers mutate the DNA and can thus corrupt the hard drive; but the package can also go wrong. Fortunately, the packaging is more reversible

than trying to do something about an actual mutation. We can do things to bring that cell back into normal balance.

-- Team Leader Stephen B. Baylin, M.D., deputy director, Sidney Kimmel Comprehensive Cancer Center

Dream Team Leaders	Leader: Stephen B. Baylin, M.D., deputy director, Sidney Kimmel Comprehensive Cancer Center (Baltimore, MD)	Co-Leader: Peter A. Jones, Ph.D., distinguished professor of urology, biochemistry and molecular biology, University of Southern California (Los Angeles, CA)
Dream Team Principals	Steven Belinsky, Ph.D., director, Lung Cancer Program, Lovelace Respiratory Research Institute (Albuquerque, NM), Nancy Davidson, M.D., director, University of Pittsburgh Cancer Institute and UPMC Cancer Centers (Pittsburgh, PA), Jean-Pierre Issa, M.D., professor, department of leukemia, University of Texas M. D. Anderson Cancer Center (Houston, TX)	
Dream Team Advocates	Diana Chingos, cancer patient advocate and chairman, Cancer Survivorship Advisory Council, University of Southern California Norris Comprehensive Cancer Center (Los Angeles, CA), Lillie Shockney, R.N., B.S., MAS, administrative director, Avon Foundation Breast Center, Johns Hopkins University (Baltimore, MD)	

Title: “An Integrated Approach to Targeting Breast Cancer Molecular Subtypes and Their ‘Resistance’ Phenotypes”

Overview:

Although a great deal of progress has been made in understanding and treating breast cancer, over 40,000 women a year lose their lives to this disease in the United States alone. During the past several years, researchers have come to understand that breast cancer is not a single disease but rather a spectrum of conditions that vary in their biology and response to treatment, and understanding breast cancer’s molecular diversity has been the driving force leading to the development of new treatments for this disease.

Researchers are rapidly moving beyond the “one size fits all” approach into a new era in which breast cancer treatments will be tailored to the biology of the tumor. This project will address the most significant issues related to the three major subtypes of breast cancer -- ER positive, HER2 positive and triple negative (ER negative, PR negative and HER2 negative) and will use that information to develop innovative, less toxic therapies with the potential to improve the treatment outcomes for women with this disease.

One of the primary obstacles to effective cancer treatment is the ability of cancer cells to become resistant to treatments that are initially effective. Over a period of time, cancer cells are able to develop ways of “outsmarting” the drugs and agents designed to kill them. This Dream Team will study the driving mechanisms that lead to resistance in the three major breast cancer subtypes. Understanding resistance opens the door to developing innovative therapeutic agents that overcome this critical problem.

Another area of interest is in the role that cancer stem cells play in resistance. Researchers now realize that the growth and spread of many cancers, including breast cancers, are influenced by the existence of these stem cells which are often highly resistant to otherwise effective treatments. The Team will study the ways in which this unique malignant cell population operate across the three major breast cancer subtypes, knowledge that could be important to the developing new treatments for breast as well as other major cancers.

One critical component of this study will be to bring together the vast amount of information that exists about breast cancer into an integrated data base that will form a “discovery platform,” or basis for identifying and validating new drug combinations and targets that can be pursued in clinical trials. The Team expects that these efforts will lead to significantly improved therapies for breast cancer, especially the most difficult to treat forms, within the three year period.

Specific Research Goals:

- Develop innovative, less toxic therapies with the potential to improve the treatment outcomes for women with the three major subtypes of breast cancer.
- Study ways in which the malignant cancer stem cells impact resistance across the three major breast cancer subtypes, important data required to develop new treatments for breast and other major cancers.

- Develop a “discovery platform” (a basis for identifying and validating new drug combinations and targets that can be pursued in clinical trials) by creating a database that integrates existing information about breast cancer.

We have spent the last several decades coming to a deep understanding of some of the events that go awry in cancers that lead to the development of malignant disease. Where we are today is at a period where we can actually fingerprint each individual tumor so know what’s wrong with it, and I think that we can use our biological understanding to decide which drugs we can use to treat that individual cancer.

-- Team Leader Joe W. Gray, Ph.D., director, Life Sciences Division, Lawrence Berkeley National Laboratory

We are at a point today where technology has really enabled us to ask questions at a sophisticated level in ways we were never able to ask before—critical questions that we have had for a long time but couldn’t approach. Now we can begin to ask what exactly is broken within a cell, what converts that normal cell to a malignant one? We can think now about how we might interfere with those pathways that cause cancer.

-- Team Leader Dennis J. Slamon, M.D., Ph.D., director of clinical/translational research at the University of California Los Angeles, Jonsson Comprehensive Cancer Center

<p>Dream Team Leaders</p>	<p>Leader: Joe W. Gray, Ph.D., director, Life Sciences Division, Lawrence Berkeley National Laboratory (Berkeley, CA)</p>	<p>Leader: Dennis J. Slamon, M.D., Ph.D., director of clinical/translational research at the University of California Los Angeles, Jonsson Comprehensive Cancer Center (Los Angeles, CA)</p>
<p>Dream Team Principals</p>	<p>Professor Alan Ashworth, FRS, Ph.D., director, Breakthrough Breast Cancer, The Institute of Cancer Research (London, UK), Joan Brugge, Ph.D., professor and chair, Cell Biology, Harvard Medical School (Boston, MA), Gregory Hannon, Ph.D., professor, Watson School of Biological Sciences, Cold Spring Harbor Laboratory (Cold Spring, NY), V. Craig Jordan, OBE, Ph.D., D.Sc., scientific director, Vincent T. Lombardi Comprehensive Cancer Center, Georgetown University [July 1] (Washington, DC), C. Kent Osborne, M.D., director, Dan L. Duncan Cancer Center and Lester and Sue Smith Breast Center, Baylor College of Medicine (Houston, TX), Max Wicha, M.D., director, University of Michigan Comprehensive Cancer Center(Ann Arbor, MI), Arul Chinnaiyan, M.D., Ph.D., director, Michigan Center for Translational Pathology, University of Michigan (Ann Arbor, MI), David Haussler, Ph.D., investigator, Howard Hughes Medical Institute (Santa Cruz, CA) Peter Sorger, Ph.D., professor, systems biology, Harvard Medical School (Boston, MA), Terry Speed, Ph.D., professor department of statistics, University of California</p>	

